MARKERS OF DISEASE RISK IN SMOKERS

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CLINICAL STUDIES

OBJECTIVE:

Assess potential for harm reduction in smokers

Prerequisites to Initiate Clinical Study:

- Evidence from smoke chemistry to support potential to reduce harm in smokers
- Evidence from toxicology studies to support potential to reduce harm in smokers

Results of Smoking Cessation

- Reduced BAL Cell Counts[1]
- Improved Visual Bronchitis Index[1]
- Decreased Hemoglobin[2]
- Decreased Hematocrit[2]
- Decreased MCV[2]
- Decreased WBC Count[2]
- Decreased Total Cholesterol[2]
- Increased HDL[2]
- Decreased LDL[2]
- Increased HDL/LDL[2]

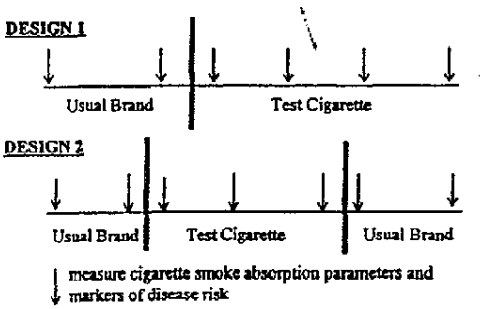
[1] Reasnard, S.L., Daughton, D.M., (1993) Smoking reduction and biological markers of response. *Monaldi Arch Chest Dis*, 48: 580-582.

[2] Lidvall-Lidfeldt, D., Blöndal, T., Fransson, M., Gudmundsson, T.V., Silwa, U. (1999) Effects of nicotine nasal spray on atherogenic and thrombotic factors during smoking cessation. *Journal of Internal Medicine*, 246:61-66.

CLINICAL STUDY DESIGNS

- Measure markers of disease risk
- Compare markers of disease risk when smoking usual brand to when smoking test cigarette
- Non-smoker group may be used as negative control

Simple Clinical Study Designs



CLINICAL STUDY DESIGNS

- Subject Selection:
  - Won't quit
  - Heavy-use smoker
  - Additional study-specific criteria
- Compliance:
  - Critically important
  - Difficult to monitor

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Source: https://www.industrydocuments.ucsf.edu/docs/ktnj0001

Biomarkers of Smoke Absorption

- Nicotine or Cotinine
  - Saliva
  - Blood Serum
  - Urine
- Carbon Monoxide
  - Exhaled Breath
  - Bound to Hemoglobin

Markers of Disease Risk

- Cardiovascular Disease
  - Atherogenic risk markers
  - Thrombogenic risk markers
- Chronic Obstructive Pulmonary Disease
  - Markers of Inflammation
- Cancer
  - Cellular morphology
  - Cell surface markers
  - Exposure to mutagens

Markers of Atherogenesis Risk

- HDL
- LDL
- Oxidized LDL
- Triglycerides
- Total Cholesterol
- HDL/LDL Ratio
- WBC Count

Markers of Thrombogenesis Risk

- Stressed Template Bleeding Time
- Fibrinogen
- Prothrombin Time
- Activated Partial Thromboplastin Time
- Plasminogen Activator Inhibitor
- Markers Affecting Viscosity
  - hematocrit
  - MCV
- Markers of Platelet Activation
  - thromboxane
  - prostacyclin

Markers of Chronic Obstructive Pulmonary Disease Risk

- Standardized Respiratory Symptom Questionnaires and/or Diaries
- Bronchoalveolar Lavage (inflammatory cells, protein, cytokines, oxidative stress markers, inflammatory mediators)
- Pulmonary Epithelial Permeability
- Surfactant Function
- Standardized Visual Bronchitis Index (redness, swelling, mucus)

Markers of Carcinogenesis Risk

- Lung Cancer

  Biopsy of Lung During BAL Procedure (field cancerization status, *e.g.*, metaplasia, cell surface markers)
- Other Cancers

  Urinary Mutagenicity (Ames *Salmonella* Assay)

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Source: https://www.industrydocuments.ucsf.edu/docs/ktnj0001

Clinical Studies on *Eclipse*

- University of Rochester Medical Center
  (4 weeks)
- University of Nebraska Medical Center
  (2 months)

Conclusions of RJRT Clinical Studies on *Eclipse*

- No consistent changes in markers of atherogenesis or thrombogenesis risk have been observed
- The following changes have been noted in markers for carcinogenesis risk:
  - urinary mutagenicity was decreased
  - pulmonary inflammation was decreased

Conclusions of RJRT Clinical Studies on *Eclipse*

- Improvement in markers for chronic obstructive pulmonary disease have been observed:
  - Improved symptomology
  - Reduced pulmonary epithelial permeability
  - Improved gene expression profile in pulmonary macrophages
  - Reduced pro-inflammatory cytokines in BAL fluid
  - Reduced number of inflammatory cells recovered by BAL
  - Decreased goblet cell metaplasia
  - Improved visual bronchitis index

SUMMARY

Clinical studies are an important component of a scientific strategy to assess the risk-reduction potential of new cigarettes

Effective Strategy for Assessing Risk Reduction in Cigarettes

Reduction of Chemical Substances
- ✓ Smoke Chemistry Studies

Less Toxicity
- ✓ *In Vitro* Toxicity Studies
- ✓ Animal Toxicity Studies

Reduced Effects in Smokers
- ✓ Smoking Behavior/Exposure Assessment
- ✓ Clinical Studies using Markers

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